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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/598,885	09/14/2006	Jakob Busch-Petersen	PU60791	1731

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EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	PAPER NUMBER
1611	

NOTIFICATION DATE	DELIVERY MODE
10/06/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

US_cipkop@gsk.com

Office Action Summary	Application No.	Applicant(s)	
	10/598,885	BUSCH-PETERSEN ET AL.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,8-10 and 13-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-4,13-26 and 28-31* is/are allowed.

6)☒ Claim(s) *6, 8-10 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on May 22, 2008.

Status of Claims

Amendment of claims 4 and 6, addition of new claims 21-26 is acknowledged.

Claims 1-4, 6, 8-10, and 13-26 are currently pending and are the subject of this office action.

In the response filed by applicant on December 14, 2007 applicant elected without traverse the following species: {4-[2-(1,4-dihydro-1,4-epiazano-naphtalen-9-yl)-ethyl]-cyclohexyl}-amide. In the office action dated February 5, 2008 and mailed on February 22, 2008 only the before mentioned species was examined. In the present office action, and since no prior art was found on the elected species, the search was expended to the remaining species which are also free of prior art

Claims 1-4, 6, 8-10, and 13-31 are currently under examination.

Priority

The present application is a 371 of PCT/US04/08025 filed on 03/17/2004.

Response to Arguments

This is in response to applicant's arguments, filed on May 22, 2008.

Claims rejected under 35 USC 112, first paragraph (enablement).

Applicant's arguments regarding claims 1-4, 13-20 (and now also 21-26) which recite a compound of formula I as in claim 1, have been fully considered and they are persuasive.

Rejection under 35 USC 112, first paragraph (enablement) is withdrawn for claims 1-4, and 13-26.

Applicant's arguments regarding claims 6, and 8-10 (and now also claim 27), which recite a method of treating a muscarinic acetylcholine receptor mediated disease with compounds of Formula I, have been fully considered but they are not persuasive.

Applicant argues that the specification describes four examples of nasal formulations as well as various inhalers that definitively point towards delivery to the lungs. This formulations do not prove whether these compounds are indeed inhibitors of any of the muscarinic acetylcholine receptors or more specifically of the M3 subtype which is required for conditions such as asthma, COPD, etc.

Applicant further argues that no examples might be required for enablement. Although this is true in certain cases, the requirement of working examples is required when the nature of the art becomes unpredictable. MPEP 2164.03 cites: "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more

predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling." Since relatively few antimuscarinic compounds are in use in the clinic (see applicant's own specification end of page 1 and beginning of page 2), and since the systemic efficiency of cholinergic drugs available is limited due to lack of selectivity (see Oppitz et. al., Expert Opinion in Therapeutical patents (2006) 16:481-491, see section 4.1 on page 486), it is safe to say that despite all the available research there is still much to be learn regarding the drugabilty of anti-muscarinic compounds. Applicant is claiming a new structure in an area where is very unpredictable whether a compound could have any efficacy in any respiratory disease. No data is provided for anti-muscarinic activity and/or selectivity, either *in-vitro* or *in-vivo*. Based on this, it is safe to say that there are enough arguments to doubt that any of the claimed compounds has the potential to be effective in the treatment of any muscarinic acetylcholine receptor mediated disease.

Rejection under 35 USC 112, first paragraph (enablement) is maintained for claims 6 and 8-10.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Allowable Subject Matter

Claims 1-4, 13-26, and 28-31 are allowed.

The closest prior art is Busch-Petersen (WO 2004/091482, common inventors). The prior art and the instant application differ by the fact that International Publication WO 2004/091482 claims compounds of formula I (see page 3) that contain partial structures that are similar, but not identical to the structures of the instant application: the compounds of formula I in the prior art do not encompass the R2 substituents of the instant application and vice versa. So the compounds of the instant application are neither anticipated nor obvious over the prior art.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6, 8-10 and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996). As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1- the quantity of experimentation necessary,

2- the amount of direction or guidance provided,

3- the presence or absence of working examples,

4- the nature of the invention,

5- the state of the prior art,

6- the relative skill of those in the art,

7- the predictability of the art, and

8- the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping

that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention

Claims 6, 8-10 and 27 recite a method of treating a muscarinic acetylcholine receptor mediated disease, selected from the group consisting of chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema and allergic rhinitis in a mammal in need thereof comprising administering to said mammal an effective amount of a compound of Formula I (see claim 1).

2. The relative skill of those in the art

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

3. The state and predictability of the art

It is well established that "the scope of enablement varies with the degree of unpredictability of the factors involved", and physiological activity is considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the

factors involved); *Nationwide Chemical Corporation, et. al. v. Wright, et. al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances); *Ex parte Sudilovsky* 21 USPQ2d 1702 (Applicant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable).

Regarding more specifically to the treatment of respiratory diseases there are very few anti-muscarinic compounds that are in use in the clinic (see applicant's specification end of page one, beginning of page 2). Also, according to Oppitz et. al. (Expert Opinion in Therapeutical patents (2006) 16:481-491, see section 4.1 on page 486): "despite the great therapeutic value of cholinergic drugs in various fields of pharmacology, the systemic efficiency of drugs available is limited due to lack of selectivity".

4. The breadth of the claims

Claims 6, 8-10 and 27 claim a very broad genus of compounds.

5. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no experimental data for any of the compounds claimed.

6. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept that the compounds of Formula I, could be predictably used as treatment for any of the respiratory diseases listed in claim 6. Since there is no precedent in the literature that any of these compounds could possibly be a muscarinic acetylcholine receptor antagonist, since they lack the structural features that the literature suggests is required for such activity, and since applicant did not provide experimental data that supports that claim; determining if the elected species (or any of the non-elected compounds), would be a useful treatment of any respiratory disease, would require testing these compounds in an *in vitro* assay to determine, which, if any, of these compounds has antimuscarinic activity, then an *in vivo* functional assay in some animal model to determine if they are efficacious against any respiratory disease, formulation into a dosage form, and subjecting into clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants.

Accordingly, the inventions of claims 6,8-10 and 27 do not comply with the enablement requirement of 35 U.S.C 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation with no assurance of success.

Conclusion

Claims 6, 8-10 and 27 are rejected, and claims 1-4,13-26 and 28-31 are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau can be reached on 571 272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/

Examiner, Art Unit 1611
September 24, 2008

/Sharmila Gollamudi Landau/

Supervisory Patent Examiner, Art Unit 1611